to 50 nt or at least about 60°C for probes comprising nucleic acids of more than 50 nt, wherein sequences at least about 85% homologous to each other remain hybridized to each other.

29. (Amended) The nucleic acid of claim 28 encoding the polypeptide of SEQ ID NO: 2, said polypeptide having epithelial cell proliferation activity.

Pursuant to 37 C.F.R. 1.121(c), a marked up version of the claims showing the changes made appears as Appendix C of this Amendment.

REMARKS

Upon entry of the present amendment, claims 1, 2, 4-5, 7-10, 14, 19-21, 28 and 29 will be pending in the application. Applicants thank the Examiner for properly restoring claim 14 to those claims currently under consideration. The Abstract has been amended as requested by the Examiner. Claims 1, 14 and 19 have been amended to more distinctly point out the subject matter being claimed. Support for amendments to claims 2 and 29 appear in the specification at least, *e.g.*, on p. 6, lines 3-7, and on p. 59, lines 7-8. Support for claim 5 amendments appears in the specification at least, *e.g.*, on page 3, lines 10-15. Support for claim 28 amendments appears in the specification at least, *e.g.*, on page 17, line 16, through page 18, line 8.

The December 12, 2002, Advisory Action indicated that the amendments in Paper 18 were not entered by the Examiner. Accordingly, applicants have filed this RCE to have the claim amendments presented here entered. No new matter has been added.

Objections to the Specification are overcome.

The Examiner objected to the Abstract. The Abstract has been amended. This objection should be withdrawn.

The Final Office Action and Advisory Action.

The outstanding rejections made by the Examiner in the September, 2002 Office Action were the following:

(1) Claims 1-2, 4-5, 7-10, 14, 19-20, 28 and 29 were rejected under 35 U.S.C. §101 as not supported by a specific, substantial and credible utility, and under 35 U.S.C. §112, first paragraph, for failing to teach how to use an invention without proper utility;

(2) Claims 14 and 29 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description;

(3) Claims 1, 3-4, 19-21, and 28 were rejected under 35 U.S.C. §112, second paragraph, for being indefinite; and

(4) Claims 5 and 28-29 were rejected under 35 U.S.C. §102(b), for being anticipated.

In the Advisory Action, the Examiner noted that the claim amendments in applicants' November 2002 response were not entered. Upon entry of the claim amendments here, Applicants believe that each of the rejections are overcome on the basis of the arguments presented in the November 18, 2002 response. In addition, applicants have presented in this Response, additional arguments to address the utility rejection (as it is stated under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph – the "how to use" rejection). A discussion of the patentability of the claims presented herein is discussed below.

35 U.S.C. § 101 Utility Rejection Is Overcome Both On Its Own, And In Combination With The 35 U.S.C. § 112, First Paragraph, Rejection.

Claims 1-2, 4-5, 7-10, 14, 19-20, 28-29 remain rejected by this Examiner as lacking utility and as being non-enabled. Specifically, the Examiner contends that because multiple utilities are recited in the specification, that no "specific" utility has been recited.

First, the record is clear that the specification makes a specific assertion of utility for the claimed invention – in this case nucleic acids encoding novel fibroblast growth factor-20 ("FGF-20"). The proteins encoded by the novel nucleic acids of this invention may be used to stimulate cell growth, including especially growth of fibroblasts and epithelial cells in the linings of the gastrointestinal tract. The specification expressly states this as a specific, substantial credible utility. See, e.g., the following sections in the disclosure:

"The proteins of the invention may be used to stimulate cell growth and cell proliferation in conditions in which such growth would be favorable. An example would be to counteract

toxic side effects of chemotherapeutic agents on, for example, hematopoiesis and platelet formation, linings of the gastrointestinal tract, and hair follicles." *See*, specification at., *e.g.*, p. 59, lines 7-10.

The specification (pp. 57-59) details stimulation of epithelial cells (including keratinocytes and fibroblasts), glial cells, and cells found in the lining of the gastrointestinal tract. *See*, *e.g.*, p. 58, lines 1-14; p. 59, lines 7 – 12. Such stimulation can be used to heal wounds and ulcers. *See*, *e.g.*, p. 58, lines 11-13.

Applicants have previously submitted unequivocal evidence of record that confirms that the proteins encoded by the claimed nucleic acids have precisely this activity. Additionally, applicants now make of record in the instant application their published work demonstrating that administration of FGF-20 protein in fact "enhances the growth of intestinal fibroblasts". See Jeffers et al., Gastroenterology, 123, pp. 1151-62 (2002) (citing Abstract) (Exhibit 1).

Moreover, applicants submit herewith a Press Release announcing the FDA approval of CuraGen's (the assignee of this application) Investigational New Drug application to initiate human clinical trials using FGF-20 to treat oral mucositis – oral mucositis is a side effect of chemotherapy and radiotherapy that results in degradation of mucosal tissue that can range from redness and irritation to severe ulcerations of the mouth and throat (Exhibit 2). In this trial, FGF-20 is being tested for ability to stimulate cell proliferation (and specifically of epithelial cells) and to counteract toxic side effects of chemotherapeutic and radiotherapeutic agents in the throat and mouth (*i.e.*, linings of the gastrointestinal tract), precisely as recited in the specification. This is all that is required.

For the record, applicants note that utility is also supported by the structural similarity of this FGF-20 with other known members of the FGF family and specifically contains a conserved family domain and hydrophobic transport domain. In addition, the FGF-20 encoded by the nucleic acids claimed here has a biological activity similar to a structurally related fibroblast growth factor-9 (FGF-9) compound already known and tested in the art for activation and/or proliferation of glial cells and fibroblasts (which are epithelial cells). *See*, specification at least at, *e.g.*, pp. 57-58 & FIG. 9. Other known FGFs have been demonstrated to be useful in the stimulation of wound healing; see, *e.g.*, U.S. Patent No. 5,804,213. Thus, one utility asserted

here, namely diagnosing and treating cell proliferation associated disorders such as epithelial cell proliferation and wound healing associated with oral mucositis for FGF-20 is supported and consistent with generally accepted scientific principles.

Finally, Applicants also submitted the Declaration of William LaRochelle filed under 37 CFR §1.132 ("LaRochelle Declaration"), in support of utility. A declaration will go to confirm a utility where, as here, the specification did in fact assert that utility when filed. *See*, Brana, 51 F.3d at 1567, n. 19. In Brana, the Court stated that a declaration can be used to substantiate the asserted utility since the declaration pertains to a statement already in the specification. Ibid. The LaRochelle Declaration should have been dispositive of the utility requirement under 35 USC §101. The LaRochelle declaration merely substantiates statements and assertions already in the specification as filed, namely that the claimed invention stimulates cell growth, including growth of epithelial cells (*e.g.*, fibroblasts and keratinocytes). *See* specification, p. 58, lines 11-13. *See* also MPEP 2107 (II)(B)(1)(ii).

The fact that multiple utilities are recited in the specification does not mean that there is lack of a specific, credible, utility. As the MPEP makes clear, "[i]t is common and sensible for an applicant to identify several specific utilities for an invention". See MPEP § 2107.01. The case law is also clear. In re Gottlieb 328 F.2d 1016 (CCPA), is particularly relevant. In Gottlieb, multiple utilities were disclosed. The Court held that one specific utility was sufficient to meet the utility requirement (328 F.2d at 1018). That is all that is required here also. And that requirement has been met here. See also In re Brana 51 F.3d 1560 (Fed.Cir).

The Examiner has also implicated a "how to use" utility-based § 112, first paragraph, rejection. This cannot stand. To uphold a utility-based § 112, first paragraph, rejection, a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555 (Fed. Cir. 1992), as discussed in the Legal Analysis accompanying the Utility Guidelines (M.P.E.P. § 2107). The only instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did." M.P.E.P. § 2107 (emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific

principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.01. That is simply not the case here -- as is plain from Jeffers paper (Exhibit 1), and the FDA's approval of the IND (Exhibit 2)

The rejection should be withdrawn.

35 U.S.C. § 112, first paragraph, rejection is overcome.

Claims 14 and 29 were rejected for enablement on the ground that those claims did specify the SEQ ID of the encoded polypeptide. The claim amendments here clarify that that encoded polypeptide is defined by SEQ ID NO:2. Upon entry of the amendments, these rejections are overcome.

The 35 U.S.C. § 112, Second Paragraph Rejections Are Overcome.

Claims 1, 3-4, 19-21 and 28 were rejected as being indefinite for various reasons. Applicants believe these rejections are moot in view of the amendments to the claims made in the November 18, 2002 amendment (not entered).

Claims 1 and 28 were rejected for recitation of "FGF-CX." The phrase has been deleted from claim 1 and does not appear in claim 28 (having been deleted in Applicants' June 28, 2002 response).

Claims 4 and 28 were rejected for reciting "hybridization ... under stringent conditions." Both claims have been amended to recite stringent hybridization conditions provided in the specification. Upon entry of the amendments, these rejections are moot.

The 35 U.S.C. § 102(b) Rejection Is Overcome.

Claims 5, 28 and 29 were rejected as being anticipated by Nauro *et al.* (U.S. Pat. No. 5,512,460) ("Nauro"). Claim 29 depends from claim 28. Applicants traverse the rejection as applied to the claims as amended. As applicants demonstrated in the November 18, 2002, response, Nauro is only about 66-68% homologous and thus does not meet the 85% homology

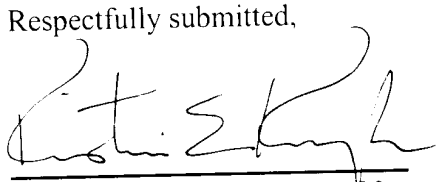
requirements of the claims as amended. For this reason, claims 5, 28 and 29 as amended cannot be anticipated by Nauro. Upon entry of the amendments, the rejection is overcome.

CONCLUSION

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

No fee is believed due at this time. The Commissioner is hereby authorized to charge payment of any filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 15966-557).

Respectfully submitted,



Dated: March 17, 2003

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PATENT TRADEMARK OFFICE

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APPENDIX A: SUBSTITUTE ABSTRACT

ABSTRACT

The present invention provides FGF-CX polypeptides and polynucleotides, and antibodies that immunospecifically bind to FGF-CX or any derivative, variant, mutant, or fragment of the FGF-CX polypeptide, polynucleotide or antibody. The invention additionally provides methods of use for a FGF-CX polypeptide, polynucleotide and antibody.

APPENDIX B: VERSION MARKED TO SHOW CHANGES MADE IN ABSTRACT

In the specification:

Amend the Abstract on page 81 as indicated below. Replace page 81 with substitute page 81 attached as Appendix A.

The present invention provides FGF-CX polypeptides and polynucleotides, and antibodies that immunospecifically bind to FGF-CX or any derivative, variant, mutant, or fragment of the FGF-CX polypeptide, polynucleotide or antibody. The invention additionally provides methods <u>of use for a</u> [in which the] FGF-CX polypeptide, polynucleotide and antibody[are used in detection and treatment of pathological states].

APPENDIX C: VERSION MARKED TO SHOW CHANGES MADE IN CLAIMS

In the claims:

Amend the claims as indicated below.

1. (Twice Amended) An isolated [FGF-CX] nucleic acid molecule encoding a polypeptide comprising a sequence of SEQ ID NO:2, or the complement of said nucleic acid molecule.

2. (Amended) The nucleic acid molecule of claim 1, wherein said nucleotide sequence encodes a polypeptide of SEQ ID NO:2, or the complement of said nucleic acid molecule, said polypeptide having epithelial cell proliferation activity.

4. (Amended) The isolated nucleic acid molecule of claim 1, said molecule hybridizing under stringent conditions to a nucleic acid sequence complementary to a nucleic acid molecule comprising the sequence of nucleotides of SEQ ID NO:1, or the complement of said nucleic acid molecule, said stringent condition comprising those in which a salt concentration is from about 0.01 M to about 1.0 M sodium ion at a pH from about 7.0 to about 8.3, and in which a temperature is at least about 30°C for probes comprising nucleic acids of 10 to 50 nt or at least about 60°C for probes comprising nucleic acids of more than 50 nt.

5. (Twice Amended) The isolated nucleic acid molecule of claim 1, said molecule encoding the amino acid sequence of SEQ ID NO:2, said amino acid sequence further comprising one or more conservative amino acid substitutions, wherein said substitutions do not alter the functional ability of the encoded FGF-CX protein, and wherein the nucleic acid molecule encodes a polypeptide at least 85% identical to the polypeptide comprising the amino acid sequence of SEQ ID NO:2.

14. (Thrice Amended) A method of producing an isolated FGF-CX polypeptide of SEQ ID NO:2, said method comprising the step of culturing the host cell of claim 10 under conditions in which the nucleic acid molecule encoding said polypeptide of SEQ ID NO:2 is expressed.

19. (Twice Amended) A [pharmaceutical] composition comprising the nucleic acid of claim 1, and a pharmaceutically acceptable carrier.

28. (Twice Amended) An isolated nucleic acid molecule comprising a nucleic acid of SEQ ID NO: 1, wherein the nucleic acid hybridizes to a nucleic acid molecule of SEQ ID NO: 1 under stringent conditions, said stringent condition comprising those in which a salt concentration is from about 0.01 M to about 1.0 M sodium ion at a pH from about 7.0 to about 8.3, and in which a temperature is at least about 30°C for probes comprising nucleic acids of 10 to 50 nt or at least about 60°C for probes comprising nucleic acids of more than 50 nt, wherein sequences at least about 85% homologous to each other remain hybridized to each other.

29. (Amended) The nucleic acid of claim 28 encoding the polypeptide of SEQ ID NO: 2[having an activity selected from the group consisting of:

a fibroblast growth factor-like activity;

a cell proliferative activity;

a glia activating activity; and

a neuroprotective-like activity]

, said polypeptide having epithelial cell proliferation activity.